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GLOBAL DYNAMICS OF A MATHEMATICAL MODEL FOR HTLV-I INFECTION OF T CELLS

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ABSTRACT. Human T-cell lymphotropic virus I (HTLV-I) infection is linked to the development of adult T-cell leukemia/lymphoma (ATL). HTLV-I infection of healthy $CD4^+$ T cells is known to take place through cell-to-cell contact with infected T cells. We consider a compartmental model for the transmission dynamics of the HTLV-I infection. The force of infection is assumed to be of a general form, and the resulting incidence term contains, as special cases, the bilinear and the standard incidences. Our mathematical analysis establishes that the global dynamics of T-cell infection are completely determined by a basic reproduction number R_0. If $R_0 \leq 1$, infected T cells always die out. If $R_0 > 1$, HTLV-I infection becomes chronic, and a unique endemic equilibrium is globally stable in the interior of the feasible region.

1 Introduction. Human T-cell lymphotropic virus I (HTLV-I) infection is linked to the development of adult T-cell leukemia/lymphoma (ATL), among many illnesses. Infection by HTLV-I is characterized by cell-to-cell infection [**1**], [**2**], [**3**] of $CD4^+$ T cells which HTLV-I preferentially infects [**4**], [**5**]. HTLV-I is a single-stranded RNA retro virus with reverse transcriptase activity that leads to a DNA copy of the viral genome. The viral DNA copy is then integrated into the DNA of the host genome. After integration, the viral DNA can latently persist within a T cell for a long period of time. The latent infected T cells contain the

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viral DNA but are not producing it, and they can not cause new infections of susceptible cells. Stimulation of the latent infected $CD4^+$ T cells by antigen can initiate activation of the infected cells. Actively-infected T cells can produce virus and can cause new infections of susceptible T cells. Actively-infected T cells may then convert to ATL cells.

To model the T-cell infection process, we partition the related cell populations into four compartments: uninfected, latently-infected, actively-infected $CD4^+$ T cells, and leukemia cells. Let T, T_L, T_A, and T_M denote the numbers of cells in the corresponding compartments. Let $N = T + T_L + T_A$ be the total number of T cells in the system that are active in the transmission of infection. Since HTLV-I infection in $CD4^+$ T cells takes place through cell-to-cell contact between actively-infected cells and uninfected (susceptible) cells, the incidence term can be modeled similarly as in the population models for infectious diseases. Two common incidence forms are the bilinear incidence $\beta T T_A$ and the standard incidence $\lambda T T_A/N$ (also called proportionate mixing incidence). Since total T-cell population N may fluctuate with time in our model, which of these two common incidence forms is more appropriate is the subject of much discussion in the literature (see [**6**]). In our model, we assume the incidence is of form $\kappa T T_A f(N)$, where κ is the infection rate which accounts for the overall effects of HTLV-I reproduction such as contact rate and infectivity, $f(N) = N^{-\varepsilon}$ with $0 \leq \varepsilon \leq 1$. When $\varepsilon = 0$ and 1, our incidence form reduces to the bilinear and the standard incidence, respectively.

We assume that $CD4^+$ T cells are produced at a constant rate Λ and newly produced T cells are susceptible. The death or removal rates for uninfected, latently-infected, actively-infected $CD4^+$ cells, and ATL cells are μ_T, μ_L, μ_A, and μ_M, respectively. The removal rates μ_A and μ_M can include the loss due to natural causes, immune response and chemotherapy. The proliferation of ATL cells are assumed to follow a classical logistic growth function: $\beta T_M(1 - T_M/T_{M_{\max}})$, where $T_{M_{\max}}$ is the maximal number that ATL cells can grow. The parameter α is the transmission rate at which latently-infected $CD4^+$ T cells become actively infected, and ρ is the transmission rate at which actively-infected $CD4^+$ T cells convert to ATL cells; thus $1/\alpha$ and $1/\rho$ can be regarded as the mean latent and infectious periods, respectively. All parameters in the model are assumed to be positive constants.

The model is described by the following system of nonlinear differen-

tial equations:

$$
\begin{aligned}
T' &= \Lambda - \mu_T T - \kappa T_A T f(N) \\
T_L' &= \kappa T_A T f(N) - (\mu_L + \alpha) T_L \\
T_A' &= \alpha T_L - (\mu_A + \rho) T_A \\
T_M' &= \rho T_A + \beta T_M \left(1 - \frac{T_M}{T_{M_{\max}}}\right) - \mu_M T_M.
\end{aligned} \tag{1}
$$

Adding up the first three equations of (1), we obtain

$$
\begin{aligned}
N' = (T + T_L + T_A)' &= \Lambda - \mu_T T - \mu_L T_L - (\mu_A + \rho) T_A \\
&\le \Lambda - \gamma(T + T_L + T_A) = \Lambda - \gamma N,
\end{aligned}
$$

where $\gamma = \min\{\mu_L, \mu_T, \mu_A + \rho\}$. It follows that $\limsup_{t\to\infty} N(t) \le \Lambda/\gamma$. Similarly, from the first equation of (1), we have $\limsup_{t\to\infty} T \le \Lambda/\mu_T$. The boundedness of T_A and the last equation of (1) lead to the logistic inequality

$$
T_M' \le \rho(\Lambda/\gamma) + \beta T_M(1 - T_M/T_{M_{\max}}) - \mu_M T_M,
$$

which implies that $\limsup_{t\to\infty} T_M \le \tilde{T}_M$, where $\tilde{T}_M$ is the positive root of the quadratic equation $\rho(\Lambda/\gamma) + \beta T_M(1 - T_M/T_{M_{\max}}) - \mu_M T_M = 0$. Thus the feasible region for (1) is

$$
\Gamma = \{(T, T_L, T_A, T_M) \in \mathbb{R}^4_+ : T \le \Lambda/\mu_T, T + T_L + T_A \le \Lambda/\gamma, T_M \le \tilde{T}_M\}.
$$

It can be shown that the region Γ is positively invariant with respect to (1).

We will prove that the global dynamics of (1) are completely determined by a basic reproduction number (or contact number)

$$
R_0 = \frac{\alpha\kappa}{(\mu_L + \alpha)(\mu_A + \rho)} \left(\frac{\Lambda}{\mu_T}\right)^{1-\varepsilon}, \tag{2}
$$

which represents the average number of secondary infections caused by a single primary actively-infected T cell introduced into a pool of susceptible T cells during its entire infection period [**7**], [**8**]. More specifically, we will establish that when $R_0 \le 1$, no chronic HTLV-I infection of T cells is possible, and the ATL cells demonstrate a typical logistic behavior: if $\beta \le \mu_M$, any ATL cells present will die out and

the only uninfected equilibrium $P_0 = (\Lambda/\mu_T, 0, 0, 0)$ is globally stable in the feasible region; if $\beta > \mu_M$, a second uninfected equilibrium $P_1 = \big(\Lambda/\mu_T, 0, 0, T_{M_{\max}}(\beta - \mu_M)/\beta\big)$ exists and is globally stable in the feasible region, and any existing ATL cells will proliferate to the carrying capacity $T_{M_{\max}}(\beta - \mu_M)/\beta$. When $R_0 > 1$, a primary HTLV-I infection in T cells always leads to chronic infection, and a unique chronic infection equilibrium $P^* = (T^*, T_M^*, T_L^*, T_A^*)$, $T^*, T_L^*, T_A^*, T_M^* > 0$, exists and is globally stable in the interior of the feasible region. Due to the chronic HTLV-I infection in the T cells, the ATL cells will proliferate to an equilibrium level T_M^* that is higher than carrying capacity $T_{M_{\max}}(\beta - \mu_M)/\beta$.

Our results generalize the global results of Wang et al. [**10**] on a HTLV-I infection model with bilinear incidence form $\kappa T T_A$, which was proposed by Stilianakis and Seydel [**9**]. Our global analysis follows that of [**10**]. The proof of the global stability of the unique chronic infection (endemic) equilibrium utilizes a geometric approach of Li and Muldowney [**11**]. The general incidence form also allows us to analyze the influence of different incidence forms.

The plan of the paper is as follows. Sections 2–4 are devoted to the global dynamics of the subsystem for the T-cell infection. In Section 5, the proliferation of the leukemia cells are analyzed and results for the full system (1) summarized. A discussion is given in Section 6.

2 The subsystem for the T-cell infection and its equilibria. The first three equations in (1)

$$\begin{aligned} T' &= \Lambda - \mu_T T - \kappa T_A T f(N) \\ T_L' &= \kappa T_A T f(N) - (\mu_L + \alpha) T_L \\ T_A' &= \alpha T_L - (\mu_A + \rho) T_A \end{aligned} \tag{3}$$

do not contain T_M, and thus can be analyzed independent of T_M. This subsystem describes the infection dynamics of T cells. We will investigate system (3) in its feasible region

$$\Delta = \left\{ (T, T_L, T_A) \in \mathbb{R}^3_+ : T \le \frac{\Lambda}{\mu_T}, T + T_L + T_A \le \Lambda/\gamma \right\},$$

which is the projection of Γ onto the (T, T_L, T_A) subspace. Let $\overset{\circ}{\Delta}$ denote the interior of Δ.

The point $Q_0 = (\Lambda/\mu_T, 0, 0)$ is an equilibrium of (3) for all parameter values. It is called the *infection-free* equilibrium. A *chronic-infection* (or

endemic) equilibrium $Q^* = (T^*, T_L^*, T_A^*)$ of (3) satisfies $T^* > 0$, $T_L^* > 0$, $T_A^* > 0$ and its coordinates satisfy the following equations:

$$
\begin{aligned}
T^* &= \frac{\Lambda}{\mu_T^*} - \frac{(\mu_L + \alpha)(\mu_A + \rho)}{\alpha \mu_T} T_A^* \\
T_L^* &= \frac{(\mu_A + \rho)}{\alpha} T_A^* \\
T^* f(N^*) &= \frac{(\mu_L + \alpha)(\mu_A + \rho)}{\alpha \kappa},
\end{aligned} \tag{4}
$$

where $N^* = T^* + T_L^* + T_A^*$. Set

$$h(x) = \frac{\Lambda}{\mu_T} - \frac{(\mu_L + \alpha)(\mu_A + \rho)}{\mu_T \alpha} x$$

$$
\begin{aligned}
&g(x) \\
&= \frac{(\mu_L + \alpha)(\mu_A + \rho)}{\kappa \alpha} \left(\frac{\Lambda}{\mu_T} + \left(1 + \frac{(\mu_A + \rho)}{\alpha} - \frac{(\mu_L + \alpha)(\mu_A + \rho)}{\mu_T \alpha} \right) x \right)^{\varepsilon} \\
&= \frac{\Lambda}{\mu_T R_0} (1 + dx)^{\varepsilon},
\end{aligned}
$$

where $d = \frac{\mu_T}{\Lambda}(1 + \frac{(\mu_A+\rho)}{\alpha} - \frac{(\mu_L+\alpha)(\mu_A+\rho)}{\mu_T \alpha})$. Then (4) can be rewritten as

$$h(T_A^*) = g(T_A^*). \tag{5}$$

Note that $h(0) = \Lambda/\mu_T$ and $g(0) = \Lambda/(\mu_T R_0) = h(0)/R_0$. Also $h(x)$ is a straight line of negative slope, $g(x)$ is increasing or decreasing depending on the sign of d.

Case I: $d \geq 0$ In this case g is non-decreasing. Graphs of g and h have no intersection point if $g(0) > h(0)$, i.e. if $R_0 < 1$, and have exactly one intersection if $g(0) \leq h(0)$, i.e. if $R_0 \geq 1$, and when $g(0) = h(0)$, i.e. when $R_0 = 1$, the only intersection is at $T_A^* = 0$.

Case II: $d < 0$ In this case g is decreasing and concave down in its domain $[0, -1/d]$. Moreover $h(x_1) = 0$ implies $x_1 = \Lambda\alpha/[(\mu_A + \rho)(\mu_L + \alpha)]$, and $g(x_2) = 0$ implies

$$x_2 = -\frac{1}{d} = \frac{\Lambda \alpha}{(\mu_A + \rho)(\mu_L + \alpha)} \cdot \frac{1}{1 - \frac{\alpha \mu_T}{(\mu_A+\rho)(\mu_L+\alpha)} - \frac{\mu_T}{\mu_L + \alpha}} > x_1.$$

Thus, the possible intersections of graphs of g and h are:

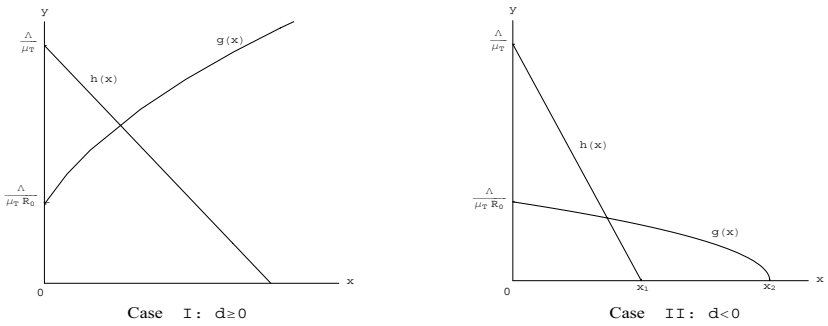

FIGURE 1: Graphs of h and g have exactly one intersection in the first quadrant when $R_0 > 1$.

(a) no intersection if $g(0) > h(0)$, namely if $R_0 < 1$;
(b) exactly one intersection if $g(0) \leq h(0)$, namely if $R_0 \geq 1$. When $g(0) = h(0)$, i.e. when $R_0 = 1$, the only intersection is at $T_A^* = 0$. See Figure 1.

In summary, we have the following proposition.

Proposition 2.1. *If $R_0 \leq 1$, system (3) has only the infection-free equilibrium Q_0. If $R_0 > 1$, there exists exactly one chronic-infection equilibrium Q^*.*

The influence of ε, and hence the incidence form, on the basic reproduction number R_0 and the equilibrium level T_A^* will be discussed in Section 6.

3 The global stability of the infection-free equilibrium Q_0 when $R_0 \leq 1$. Consider a Lyapunov function $L = (\mu_T + \alpha)T_A + \alpha T_L$, we have

$$\begin{aligned} L' &= (\mu_T + \alpha)T_A' + \alpha T_L' = T_A[\alpha\kappa T f(N) - (\mu_T + \alpha)(\mu_A + \rho)] \\ &= T_A(\mu_T + \alpha)(\mu_A + \rho)\left(\frac{\alpha\kappa T f(N)}{\mu_T + \alpha)(\mu_A + \rho)} - 1\right) \\ &\leq T_A(\mu_T + \alpha)(\mu_A + \rho)(R_0 - 1) \leq 0, \quad \text{if } R_0 \leq 1. \end{aligned}$$

The maximal compact invariant set in $\{(T, T_L, T_A) \in \Delta : L' = 0\}$ is the singleton $\{Q_0\}$ when $R_0 \leq 1$. The global stability of Q_0 follows from the LaSalle Invariance Principle [**12**].

Furthermore, if $R_0 > 1$, then $L' > 0$ for those points in $\overset{\circ}{\Delta}$ that are sufficiently close to Q_0. Solutions starting sufficiently close to Q_0 leave a neighborhood of P_0 except that on the invariant T-axis, where solutions converge to the infection-free equilibrium Q_0. In particular, the largest compact invariant set on the boundary of Δ is the singleton $\{Q_0\}$. By a standard uniform-persistence result for population models, such a boundary behaviour implies that system (3) is *uniformly persistent* in $\overset{\circ}{\Delta}$ (see [**13**], [**14**]), namely, there exists $c > 0$ such that all solutions $\big(T(t), T_L(t), T_A(t)\big)$ of (3) satisfy

$$\liminf_{t\to\infty} T(t) > c, \quad \liminf_{t\to\infty} T_L(t) > c, \quad \text{and} \quad \liminf_{t\to\infty} T_A(t) > c,$$

provided $\big(T(0), T_L(0), T_A(0)\big) \in \overset{\circ}{\Delta}$. We thus have established the following result. The proof of uniform persistence is similar to that of Proposition 3.3 in [**15**].

Theorem 3.1. *If $R_0 \le 1$, then the infection-free equilibrium Q_0 is globally stable in the closed region Δ. If $R_0 > 1$, then Q_0 is unstable and system* (3) *is uniformly persistent in $\overset{\circ}{\Delta}$.*

Biologically, the uniform persistence characterizes chronic HTLV-I infection of T cells. Theorem 3.1 establishes the basic reproduction number R_0 as a sharp threshold parameter; when $R_0 \le 1$, HTLV-I infection of T cells always dies out, whereas if $R_0 > 1$, the HTLV-I infection becomes chronic.

4 Global stability of the chronic-infection equilibrium Q^* when $R_0 > 1$. By Theorem 3.1, if $R_0 > 1$, the HTLV-I infection of T cells becomes chronic. Regarding the fashion in which the infection persists, we establish in this section that, when $R_0 > 1$, the infection eventually stabilizes at an equilibrium level. More specifically, we have the following result.

Theorem 4.1. *If $R_0 > 1$, then the unique chronic-infection equilibrium Q^* is globally stable in $\overset{\circ}{\Delta}$.*

Proof. We will apply the general method of Li and Muldowney (see Theorem 7.1 in Appendix C) to establish the global stability of Q^*. To see that system (3) satisfies the assumptions (H_1) and (H_2) of Theorem 7.1, we first note that uniform persistence of (3), together with the

boundedness of solutions, implies the existence of a compact absorbing set in $\overset{\circ}{\Delta}$ (see [**13**]). This verifies the assumption (H_2). Since Q^* is the only equilibrium in $\overset{\circ}{\Delta}$, the assumption (H_1) also holds for system (3). To apply Theorem 7.1, we construct a 3×3 matrix-valued function P, and choose a suitable vector norm $|\cdot|$ in $\mathbb{R}^3 \cong \mathbb{R}^{\binom{3}{2}}$ such that the corresponding Lozinskiĭ measure μ and $\bar{q}_2$ in (12) satisfies $\bar{q}_2 < 0$.

The Jacobian matrix J of (3) along a solution (T, T_L, T_A) is

$$\begin{pmatrix} -\mu_T-\kappa TT_Af'(N)-\kappa T_Af(N) & -\kappa TT_Af'(N) & -\kappa Tf(N)-\kappa TT_Af'(N) \\ \kappa Tf(N)+\kappa TT_Af'(N) & \kappa TT_Af'(N)-(\mu_L+\alpha) & \kappa Tf(N)+kTT_Af'(N) \\ 0 & \alpha & -(\mu_A+\rho) \end{pmatrix}$$

and its second additive compound matrix $J^{[2]} = -(\mu_T+\mu_L+\mu_A)I_{3\times 3} + \Psi$, see Appendix B, where Ψ is the following matrix

$$\begin{pmatrix} \mu_A-\alpha-\kappa T_Af(N) & \kappa Tf(N)+\kappa TT_Af'(N) & -\kappa Tf(N)-\kappa TT_Af'(N) \\ \alpha & \mu_L-\rho-\kappa TT_Af'(N)-\kappa T_Af(N) & -\kappa TT_Af'(N) \\ 0 & \kappa TT_Af'(N)+\kappa T_Af(N) & \mu_T-(\alpha+\rho)+\kappa TT_Af'(N) \end{pmatrix}.$$

Choose a matrix $P = P(T, T_L, T_A) = \operatorname{diag}(1, T_L/T_A, T_L/T_A)$. Then $P_fP^{-1} = \operatorname{diag}\{0, T_L'/T_L - T_A'/T_A, T_L'/T_L - T_A'/T_A\}$, and the matrix $B = P_fP^{-1} + PJ^{[2]}P^{-1}$ can be written in block form as

$$\begin{pmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{pmatrix}$$

where $B_{11} = -\mu_T - (\mu_L+\alpha) - \kappa T_Af(N)$, $B_{21} = (\alpha T_L/T_A, 0)^*$,

$$B_{12} = \left(\big(\kappa Tf(N) + \kappa TT_Af'(N)\big)\frac{T_A}{T_L}, \big(-\kappa Tf(N) - \kappa TT_Af'(N)\big)\frac{T_A}{T_L} \right)^*,$$

and B_{22} is given by

$$\begin{pmatrix} -\mu_T - (\mu_A+\rho) - \kappa TT_Af'(N) & \\ \quad - \kappa T_Af(N) + \frac{T_L'}{T_L} - \frac{T_A'}{T_A} & -\kappa TT_Af'(N) \\ & -(\mu_L+\alpha) - (\mu_A+\rho) \\ [13pt]\kappa TT_Af'(N) + \kappa T_Af(N) & \quad + \kappa TT_Af'(N) + \frac{T_L'}{T_L} - \frac{T_A'}{T_A} \end{pmatrix}.$$

Here $*$ denotes the transposition. Choose a vector norm in $\mathbb{R}^3$

$$|(x, y, z)| = \max\{|x|, |y| + |z|\}$$

and let μ denote the corresponding Lozinskiĭ measure, see Appendix A. We have the estimate (see [**17**], [**16**])

$$\mu(B) \le \max\{g_1, g_2\}, \tag{6}$$

where

$$g_1 = \mu_*(B_{11}) + |B_{12}|, \quad g_2 = |B_{21}| + \mu_*(B_{22}),$$

and $\mu_*(B_{11}) = -\mu_T - (\mu_L + \alpha) - \kappa T_A f(N)$,

$$\mu_*(B_{22}) = \frac{T_L'}{T_L} - \frac{T_A'}{T_A} - (\mu_A + \rho) + \max\{-\mu_T, -(\mu_L + \alpha)\}.$$

Note that $f(x) = x^{-\varepsilon}$ ($\epsilon \in [0,1]$) satisfies $f'(x) \le 0$ and

$$|xf'(x)| \le f(x)$$

for $x > 0$, we have $\kappa T f(N) + \kappa T T_A f'(N) \ge 0$. Therefore

$$|B_{12}| = |\kappa T f(N) + \kappa T T_A f'(N)|\frac{T_A}{T_L} = \big(\kappa T f(N) + \kappa T T_A f'(N)\big)\frac{T_A}{T_L}.$$

Also, $|B_{21}| = \alpha T_L / T_A$. Rewrite the second equation in (3) as

$$\frac{T_L'}{T_L} = \kappa T f(N)\frac{T_A}{T_L} - (\mu_T + \alpha)$$

and substitute into g_1, we obtain

$$\begin{aligned} g_1 &= -\mu_T - (\mu_L + \alpha) - \kappa T_A f(N) + \big(\kappa T f(N) + \kappa T T_A f'(N)\big)\frac{T_A}{T_L} \\ &= -\mu_T + \frac{T_L'}{T_L} - \kappa T_A f(N) + \kappa T T_A f'(N)\frac{T_A}{T_L} \qquad (7) \\ &\le -\mu_T + \frac{T_L'}{T_L}. \end{aligned}$$

Rewrite the third equation in (3) as

$$\frac{T_A'}{T_A} = \alpha\frac{T_L}{T_A} - (\mu_A + \rho)$$

and substitute into g_2, we have

$$
\begin{aligned}
g_2 &= \alpha\frac{T_L}{T_A} - (\mu_A+\rho) + \frac{T_L'}{T_L} - \frac{T_A'}{T_A} + \max\{-\mu_T, -(\mu_L+\alpha)\} \\
&= \frac{T_L'}{T_L} - \min\{\mu_T, \mu_L+\alpha\}.
\end{aligned} \tag{8}
$$

Relations (6), (7), and (8) imply $\mu(B) \leq \frac{T_L'}{T_L} - \delta$, where $\delta = \min\{\mu_T, \mu_L+\alpha\} > 0$. Let $K \subset \overset{\circ}{\Delta}$ be the compact absorbing set. Then there exists $\bar{t} > 0$ such that $\big(T(0), T_L(0), T_A(0)\big) \in K$ implies $\big(T(t), T_L(t), T_A(t)\big) \in K$ for all $t > \bar{t}$. Therefore, for $t > \bar{t}$,

$$
\frac{1}{t}\int_0^t \mu(B)\,ds \leq \frac{1}{t}\log\frac{T_L(t)}{T_L(\bar{t})} + \frac{1}{t}\int_0^{\bar{t}} \mu(B)\,ds - \delta\frac{t-\bar{t}}{t},
$$

for all $\big(T(0), T_L(0), T_A(0)\big) \in K$, which implies $\bar{q}_2 \leq -\delta/2 < 0$, proving Theorem 4.1. □

5 Proliferation of ATL cells and the global dynamics of (1). The proliferation of ATL cells is determined by the equation

$$
T_M' = \rho T_A + \beta T_M\left(1 - \frac{T_M}{T_{M_{\max}}}\right) - \mu_M T_M. \tag{9}
$$

With the information on the T-cell dynamics obtained in the previous two sections, we can determine the fate of the ATL cells and the global dynamics of (1). This is carried out in two different cases: $R_0 \leq 1$ or $R_0 > 1$.

When $R_0 \leq 1$, the infected T-cell population dies out, by Theorem 3.1. In particular, $T_A \to 0$ exponentially as $t \to \infty$. This implies that the dynamics of T_M satisfy the following logistic equation

$$
T_M' = \beta T_M\left(1 - \frac{T_M}{T_{M_{\max}}}\right) - \mu_M T_M.
$$

Therefore, if $\beta \leq \mu_M$, then $T_M \to 0$ as $t \to \infty$ for all nonnegative initial conditions. This and Theorem 3.1 imply that the equilibrium $P_0 = (\Lambda/\mu_T, 0, 0, 0)$ is globally stable in Γ. If $\beta > \mu_M$, then $T_M \to T_M^c = T_{M_{\max}}(\beta-\mu_M)/\beta$, the carrying capacity of T_M, as $t \to \infty$, for all positive initial conditions. Correspondingly, solutions of (1) with positive initial conditions in Γ converges to the equilibrium $P_1 = (\Lambda/\mu_T, 0, 0, T_M^c)$. We summarize the global dynamics of system (1) when $R_0 \leq 1$ in the following theorem.

Theorem 5.1. *Assume that $R_0 \leq 1$. Then*

(1) *If $\beta \leq \mu_M$, then $P_0 = (\Lambda/\mu_T, 0, 0, 0)$ is the only equilibrium of (1) and is globally stable in Γ.*
(2) *If $\beta > \mu_M$, then (1) has two equilibria P_0 and $P_1 = (\Lambda/\mu_T, 0, 0, T_M^c)$ in Γ. P_0 is unstable and P_1 is globally stable in $\Gamma \setminus \{(T, 0, 0, 0) : 0 \leq T \leq \Lambda/\mu_T\}$.*

When $R_0 > 1$, the HTLV-I infection is chronic, by Theorem 4.1. In particular, $T_A \to T_A^*$ exponentially as $t \to \infty$. Thus, the dynamics of ATL cells T_M satisfy the forced logistic equation

$$T_M' = \rho T_A^* + \beta T_M \left(1 - \frac{T_M}{T_{M_{\max}}}\right) - \mu_M T_M.$$

Simple phase-line analysis of this equation shows that T_M converges to the unique positive equilibrium T_M^* as $t \to \infty$ for all nonnegative initial conditions. Combining this with Theorem 4.1, we complete the determination of the global dynamics of (1) when $R_0 > 1$.

Theorem 5.2. *Assume that $R_0 > 1$. Then the unique endemically-infected equilibrium P^* is globally stable in $\overset{\circ}{\Gamma}$.*

Theorems 5.1 and 5.2 completely determine the global dynamics of (1). If $R_0 \leq 1$, all infected T cells die out. The fate of the ATL cells that are present is determined by a simple logistic equation; they die out if death rate μ_M dominates the proliferation rate β; or proliferate to their carrying capacity at $T_{M_{\max}}(\beta - \mu_M)/\beta$ if $\mu_M \leq \beta$. If $R_0 > 1$, any HTLV-I infection of the T cells will become chronic, both infected T cells and ATL cells persist if present. In this case, due to the chronic T-cell infection, the equilibrium level of the ATL cell proliferation, T_M^*, is higher than the carrying capacity $T_{M_{\max}}(\beta - \mu_M)/\beta$.

6 Conclusion and discussion. In this paper, we present a complete mathematical analysis for the global dynamics of a model for the infection of $CD4^+$ T cells by HTLV-I virus and progression of ATL. In the model, the $CD4^+$ T-cell population is partitioned into three subclasses: uninfected (susceptible) T, latently-infected (infected but not yet infectious) T_L, and actively-infected (infectious) T_A. The infection is through direct contact with actively-infected T cells. After infection, a T cell stays latent for a period of time, then becomes actively-infected. The actively-infected T cells may eventually convert to ATL cells.

The model is similar to that considered in [**9**] and [**10**]. The major difference is that the incidence form in our model is of a general form $\kappa T T_A f(N)$, where κ is the infection rate and $f(N) = N^{-\varepsilon}$ with $0 \leq \varepsilon \leq 1$. When $\varepsilon = 0$, our incidence form reduces to the bilinear incidence used in [**9**] and [**10**], and when $\varepsilon = 1$, it gives the standard incidence.

Our analysis establishes that the global dynamics of the model with this general incidence form is similar to that established in [**10**] for the bilinear incidence. More specifically, whether a chronic infection of the T cells by HTLV-I is possible depends completely on the value of the basic reproduction number R_0, given in (2), for the T-cell dynamics. No chronic HTLV-I infection is possible if $R_0 \leq 1$, and infected T cells always die out. An HTLV-I infection becomes chronic if $R_0 > 1$, and a unique chronic-infection equilibrium is globally stable in this case.

Correspondingly, the two different outcomes of the T-cell dynamics influence the saturated level of the ATL progression. If $R_0 \leq 1$, chronic HTLV-I infection of the T cells is not possible, the growth of the ATL cells follows a simple logistic growth, and the saturation level of the ATL cells is at most its carrying capacity $T_M^c = T_{M_{\max}}(\beta - \mu_M)/\beta$. If $R_0 > 1$, the HTLV-I infection becomes chronic, the persistence level of the ATL cells is given by the positive root of the equation

$$\beta T_M^2 - T_{M_{\max}}(\beta - \mu_M) T_M - \rho T_A^* T_{M_{\max}} = 0, \tag{10}$$

which is higher than the carrying capacity T_M^c, due to the contribution from actively-infected T cells.

We would like to observe how R_0 and T_A^* and T_M^* change with different choices of ε, namely, the force of infections. Assuming that all the parameters are kept fixed, except ε, and we let ε to increase from 0 to 1. Since it is plausible that $\Lambda/\mu_T > 1$, we can see from (2) that R_0 decreases while ε increases. Furthermore, it is plausible that the removal rate μ_T of healthy T-cells is smaller than μ_L and μ_A, we have, at the chronic-infection equilibrium,

$$\frac{\Lambda}{\mu_T} > N^* = T^* + T_L^* + T_A^* = \frac{\Lambda}{\mu_T}(1 + dT_A^*),$$

see the analysis in Section 2. This implies $d < 0$, and hence T_A^* increases as ε increases, by analyzing the intersection of the graphs of g and h as shown in Figure 1 (Case II). It follows from the quadratic equation (10) that T_M^* increases as ε increases. In summary, with the force of infection given by $\kappa T_A/N^\varepsilon$ and all other parameters kept fixed, an increase in ε lowers the basic reproduction number of the HTLV-I infection, but

increases the equilibrium level of the actively-infected T cells and that of the ATL cells. Our model and analysis, when fitted with experimental data, may be used to identify an appropriate power ε in the force of infection, for HTLV-I infection of T cells. It is worthy pointing out that, for epidemics in human populations, experimental data seems to indicate that $\varepsilon = 1$, namely the standard incidence, is more realistic (see [**8**], [**18**], [**7**]).

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Appendix A: Lozinskiĭ measures. Let $|\cdot|$ denote a vector norm in $\mathbf{R}^n$ and the corresponding matrix norm it induces. The *Lozinskiĭ measure* μ on matrices with respect to $|\cdot|$ is defined by (see [**17**]),

$$\mu(A) = \lim_{h \to 0^+} \frac{|I + hA| - 1}{h}$$

for an $n \times n$ matrix A. For properties and calculations of Lozinskiĭ measures we refer the reader to [**17**].

Appendix B: The second additive compound matrix. Let A be a linear operator on $\mathbb{R}^n$ and also denote its matrix representation with respect to the standard basis of $\mathbb{R}^n$. Let $\wedge^2\mathbb{R}^n$ denote the exterior product of $\mathbb{R}^n$. A induces canonically a linear operator $A^{[2]}$ on $\wedge^2\mathbb{R}^n$: for $u_1, u_2 \in \mathbb{R}^n$, define

$$A^{[2]}(u_1 \wedge u_2) := A(u_1) \wedge u_2 + u_1 \wedge A(u_2)$$

and extend the definition over $\wedge^2\mathbb{R}^n$ by linearity. The matrix representation of $A^{[2]}$ with respect to the canonical basis in $\wedge^2\mathbb{R}^n$ is called the *second additive compound matrix* of A. This is an $\binom{n}{2} \times \binom{n}{2}$ matrix and satisfies the property $(A + B)^{[2]} = A^{[2]} + B^{[2]}$. In the special case when $n = 2$, we have $A^{[2]}_{2\times 2} = \operatorname{tr} A$. In general, each entry of $A^{[2]}$ is a linear expression of those of A. For instance, when $n = 3$, the second additive

compound matrix of $A = (a_{ij})$ is

$$A^{[2]} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix}.$$

For detailed discussions of compound matrices and their properties we refer the reader to [**19**]. A comprehensive survey on compound matrices and their relations to differential equations is given in [**20**].

Appendix C: A general global-stability result of Li and Muldowney. We quote a general method of Li and Muldowney for proving global stability, which is used in the proof of Theorem 4.1 in Section 4. For a detailed presentation of the result of Li and Muldowney, see [**11**].

Let $\Omega \subset \mathbf{R}^n$ be an open subset and $f\colon \Omega \to \mathbf{R}^n$ be a C^1 function. Consider the differential equation

$$x' = f(x). \tag{11}$$

A equilibrium $\bar{x}$ of (11) is said to be *globally stable* in Ω if it is locally stable and all trajectories in Ω converge to $\bar{x}$. Let $x(t, x_0)$ denote the solution of (11) satisfying $x(0, x_0) = x_0$ and $Df(x)$ the Jacobian matrix of f at x. Assume that (11) satisfies the following two conditions:

(H_1) System (11) has a unique equilibrium $\bar{x}$ in Ω.
(H_2) System (11) has a compact absorbing set $K \subset \Omega$.

Let $x \mapsto P(x)$ be an $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 on Ω. Assume that $P^{-1}(x)$ exists and is continuous for $x \in K$. For a Lozinskiĭ measure μ (see Appendix A), a quantity $\bar{q}_2$ is defined as

$$\bar{q}_2 = \limsup_{t\to\infty} \sup_{x_0 \in K} \frac{1}{t} \int_0^t \mu\Big(B\big(x(s, x_0)\big)\Big)\, ds, \tag{12}$$

where

$$B = P_f P^{-1} + P(Df)^{[2]} P^{-1} \tag{13}$$

and the matrix P_f is obtained by replacing each entry p_{ij} in P by its directional derivative in the direction f, $\nabla p_{ij}^* f$. The matrix $Df(x)^{[2]}$ is the *second additive compound matrix* of the Jacobian matrix $Df(x)$ (see Appendix B). It is an $\binom{n}{2} \times \binom{n}{2}$ matrix.

The following global-stability result is due to Li and Muldowney (see [**11,** Theorem 3.5]).

Theorem 7.1 (Li and Muldowney). *Assume that Ω is simply connected and that the assumptions (H_1) and (H_2) hold. Then $\bar{x}$ is globally stable in Ω if there exists a function $P(x)$ and a Lozinskiĭ measure μ such that $\bar{q}_2$ defined in* (11) *satisfies $\bar{q}_2 < 0$.*

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